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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,028	06/22/2006	Nobuyuki Takakura	1254-0318PUS1	4443

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EXAMINER
KIM, TAEYOON

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
12/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/584,028	TAKAKURA ET AL.	
	Examiner	Art Unit	
	TAEYOON KIM	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-27* is/are pending in the application.

4a) Of the above claim(s) *20-22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19,23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/2009 has been entered.

Claim 20-22 and 24 have been withdrawn from consideration as being drawn to non-elected subject matter, claims 1-11 are canceled, and claim 27 is newly added. Claims 12-19, 23 and 25-27 have been considered on the merits. All arguments have been fully considered.

The claim rejection under 35 U.S.C.§103 to claims 12-19, 23, 25 and 26 has been withdrawn due to the amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-19, 23, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims disclose the method of differentiating mammalian bone marrow cells or cord blood-derived cells into myocardial precursor cells or myocardial cells by culturing the cells with fat cells isolated from mammalian fat tissues or a culture supernatant.

The current amendment introduces a new limitation of "fat cells isolated from mammalian fat tissues", which is narrower limitation than the original disclosure of "cells isolated from mammalian fat tissues". According to the specification, the cells isolated from fat tissues include fat cells, fat precursor cells, and somatic stem cells (p.6, lines 11-12). Therefore, the term "fat cells" in this context is considered as adipocytes.

The specification, however, discloses no adequate support that only "fat cells" used in the method of claimed invention. Rather the specification discloses the cells derived from fat tissues, which includes fat cells, fat precursor cells and somatic stem cells, are used in the claimed method.

Therefore, the new limitation of using "fat cells" in the current amendment introduces a new matter to the application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-16, 18, 19, 23, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 4,963,489).

Naughton et al. teach a method of co-culturing bone marrow cells and stromal cells including adipocytes (fat cells) (see abstract; col. 2, lines 55-66). Throughout the disclosure of Naughton et al., serum is disclosed as a constituent of culture medium (col. 18, lines 26-30; col. 19, lines 19-22; etc.).

Naughton et al. also teach the addition of growth factors and regulatory factors including epidermal growth factor (EGF) may be used to enhance, alter or modulate proliferation and cell maturation in the cultures (col. 12, lines 14-28).

Naughton et al. teach that the co-culture system comprising bone marrow cells and stromal cells comprising adipocytes appears to maximize the proliferation of multipotential hematopoietic stem cells (col. 15, lines 49-55).

With regard to the limitation of claim 25 that bone marrow cells and fat cells are from the same species, Naughton et al. teach that the bone marrow cells and stromal cells can be derived from allogeneic sources (col. 19, last line through col. 20, line 2), and thus, the sources are from the same species.

Naughton et al. do not teach the intended purpose of the claimed method directed to differentiating bone marrow cells into myocardial precursor cells or myocardial cells. However, this preamble is not considered as a limitation to be carried out in the claimed invention.

M.P.E.P. § 2111.02 reads, "If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." As such, the limitation "differentiating bone marrow cells into myocardial precursor cells" does not affect the patentability of the claimed method. Methods are defined by their constituent steps, not by an intended use or application.

With regard to the limitation of ratio between bone marrow cells and fat tissue derived cells being 1:1 to 1:10 in claim 18 or 1:4 as in claim 26, it would have been obvious to a person of ordinary skill in the art to modify the ratio of the cells by routine experimentation. Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. *In re* Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931,24 USPQ 52; *In re* Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. *In re* Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; *In re* Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and

utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. *In re* Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; *In re* Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; *In re* Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Umezawa et al. (of record) in view of Rangappa et al. (of record) in further view of Egger et al. (of record).

It is noted that the instant claim has a transition phrase of "consisting essentially of". M.P.E.P. § 2111.03 clearly indicates that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original). "A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a 'comprising' format." *PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998), *et al.* For the purposes of searching for and applying prior art under 35 U.S.C. §§ 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's

invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964) *et al.* Since the specification in this case does not particularly point out the basic and novel characteristics of the claimed composition, "consisting essentially of" in claim 27 has been interpreted as "comprising" for the purpose of art rejections.

Umezawa et al. teach a method of differentiating multipotential stem cells from bone marrow or umbilical cord blood derived cells into cardiomyocyte in vitro (par. 11, 12, 17-19).

Umezawa et al. do not teach co-culture of fat tissue derived cells or a culture supernatant of the fat tissue-derived cells with bone marrow cells or cord blood derived cells, respectively.

Rangappa et al. teach a method of differentiating fat-derived mesenchymal stem cells (MSCs) into cardiomyocytes (Abstract).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to combine bone marrow or cord blood derived multipotential stem cells of Umezawa et al. with adipose-derived stroma stem cells of Rangappa et al. in the method of myocardial differentiation of the MSCs. This is because the method of differentiating bone-marrow or cord-blood derived mesenchymal stem cells into cardiomyocytes of Umezawa et al. is identical to the method of differentiating adipose-derived stromal MSCs of Rangappa et al. such that both methods utilize 5-azacytidine to induce the mesenchymal stem cells into cardiomyocytes (par. 12 and 43 of Umezawa et al., and p.776, right col. of Rangappa et al.). Since both bone marrow or cord blood derived multipotential stem cells and fat-tissue derived MSCs can be differentiated into cardiomyocytes upon the treatment with 5-azacytidine (a cardiomyogenic differentiating factor), the combined stem cell populations would be also differentiated into cardiomyocytes under the same method steps.

It is well established that duplicating components with similar functions within a composition is obvious; see *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) and M.P.E.P. § 2144.04. The multipotential stem cells of bone marrow or cord blood, and MSCs of fat tissue are considered to have similar functions to differentiate into cardiomyocytes, it would have been obvious to combine two cell populations in the method of differentiating into cardiomyocytes.

Since the method of Umezawa et al. in view of Rangappa et al. utilize 5-azacytidine, this is considered to satisfy the new limitation of a condition which induces bone marrow cells or cord blood-derived cells to myocardial cells.

With regard to the limitation of "without genetic engineering", the treatment with 5-azacytidine to the mesenchymal stem cells is not considered as a genetic engineering. Rather it is considered as epigenetic modification since 5-azacytidine is a DNA methylation inhibitor according to Egger et al. (Abstract and Table 2).

With regard to the limitation of using a culture supernatant of fat tissue-derived cells in the method of differentiating bone marrow cells or cord blood-derived cells, Umezawa et al. teach that the differentiation of cells having a potential to differentiate into cardiomyocytes can be induced by a culture supernatant of such cells (par. 105, 106, 132). Since the fat tissue-derived MSCs of Rangappa et al. is considered as a cells having a potential to differentiate into cardiomyocytes, it would have been obvious to a person of ordinary skill in the art to use a cell culture supernatant of MSCs derived from fat tissues of Rangappa et al. in the method of Umezawa et al. utilizing a culture supernatant in induction of differentiation of bone marrow cells or cord blood-derived cells into cardiomyocytes.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

In the response to the previous OA, applicant alleged that bone marrow cells of Umezawa and fat tissue-derived stem cells of Rangappa require a chemical stimulus using 5-azacytidine, whereas cells derived from fat tissue can spontaneously differentiate into cardiomyocytes without 5-azacytidine, and bone marrow cells cannot differentiate into cardiomyocytes without any stimuli citing two references by Yamada et al. Applicant then concluded that a person of ordinary skill in the art would have not expected before applicant's invention that bone marrow cells could have differentiated into cardiomyocytes without chemical stimuli, and since the claimed co-culture method, which does not require 5-azacytidine, is an unexpected result.

This argument has been fully considered but found not persuasive. The instant claims do not particularly disclose that the claimed method does not require chemical stimuli, rather the current claims have a negative limitation of "without genetic engineering", which is different from the allegation of applicant that the claimed invention does not require the chemical stimuli, and thus, the argument is relied on features not claimed in the instant invention. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As discussed in the previous OA, the addition of a chemical stimulus, i.e. 5-azacytidine,

is not considered as "genetic engineering", and thus, such chemical stimulus is not excluded from the claimed method. Based on this, the argument that fat derived cells can spontaneously differentiate into cardiomyocytes is not considered as unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAEYOON KIM whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 5:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taeyoon Kim/
Primary Examiner, Art Unit 1651